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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/153,133	09/15/1998	D. DUKE LEE	04712/018002	5068

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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/153,133	LEE ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-54 and 56-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-54 and 56-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed on March 24, 2005 has been entered. Claims 45-54, 56-72 are pending. Any rejection that is not addressed in this Office Action is considered obviated in view of the claim amendments.

Priority

2. Priority of the instant application as set forth in Paper No. 6 is September 15, 1998.

Double Patenting

3. Claims 45-54, 56-72 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,214,368. Although the conflicting claims are not identical, they overlap in scope for the reasons of record.

4. Claims 45-54, 56-72 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,117,456 and claims 1-12 of U.S. Patent 5,683,461 for the reasons of record.

Examiner acknowledges the Applicant's intention to file a terminal disclaimer to overcome these rejections.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 45-46, 58-61, 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld US Patent 4,016,252 in view of Poser US Patent 5,968,253.

The instant claims are directed to vaccine formulations comprising a calcium phosphate and an immunogen wherein the formulation is a hardenable, injectable paste having a solid content of greater than or equal to 40%wt.

Relyveld teaches the state of art for using calcium phosphate to improve the efficacy of vaccine formulations. Reyvald teaches injectable gel calcium phosphate vaccine formulations comprising an immunogens from various bacteria and viruses (see abstract, col 2, lines 1-5, col 3-4). The calcium to phosphate ratio in gel formulation of Relyveld is from 1.62 to 1.85 (abstract, col 2 lines 1-15, col 3-4). Reyveld also teaches the use of other conventional adjuvants such as aluminum hydroxide or phosphate. (see col 2, lines 6-10). Therefore, Reyveld teaches the appropriate range of calcium and phosphate concentrations in the final formulation. Reyvald lacks in teachings a paste formulation having about 40% solid content.

Poser discloses extended release paste-like flowable injectable compositions comprising 60-95% tricalcium phosphate, a second calcium phosphate source such as monocalcium phosphate monohydrate in a powder form, in combination with an antibiotic and an aqueous injectable lubricant (see abstract, col 6, lines 48-67; col 13, lines 19-51). Poser's tricalcium phosphate meets the limitation of the instant calcium phosphate. The tricalcium phosphate of Poser is present in dry amount above the 40% by weight of the composition. Such amounts meet solid content of the instantly claimed composition. Poser formulates a depot delivery system to provide extended release

exposure of the agent of choice into the system (see col 7, lines 1-20). Poser's monocalcium phosphate monohydrate meets the limitation of the instant adjuvant. Poser meets all functional limitations of the instantly claimed composition.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify the physical characteristics of Relyveld's formulation according to the teachings of Poser and change the gel formulation of Reyveld's vaccine to a paste-like formulation by routine experimentations to optimize the described calcium phosphate concentrations. One of ordinary skill in the art would have been motivated to modify Relyveld's gel formulation into paste to formulate a depot extended release.

6. Claims 49-54, 56-57, 64-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld US Patent 4,016,252 in view of Poser US Patent 5,968,253 as applied to claims 45-46, 58-61, 72 and further in view of Classen.

The combined teachings of Reyveld and Poser are described above. Reyveld allows for the use of suitable adjuvants such as aluminum hydroxide or calcium phosphates (col 2, lines 6-10). Reyveld and Poser however do not teach the explicit use of an additional adjuvant and/or cytokine in their combination.

Classen is used to provide general knowledge in the art of vaccine formulations. Classen teaches the use of various cytokines in combination with an immunogenic agent to enhance the clinical response. (col 17, lines 6-67). Classen specifically states that a group of immune modulators, namely cytokines, are "immunocyte receptor ligands" that are capable of binding to cell receptors of immune mediator cells in a non-

antigen specific manner to cause the induction of immune response. (col 17, lines 5-16). Specifically, Classen states that they use of cytokines in a vaccine formulation improves its efficacy because cytokines modulate target cells by interacting with cytokine receptors on the target cells (see col 17, lines 48-55).

Classen also describes the use of such carrier systems that include depot adjuvants such as aluminum hydroxide and calcium phosphate salts to prolong the release of immunogenic agent. (see col 20, lines 40-50). Classen teaches vaccines for inducing an immunologic response in humans comprising an immunogen and a depot adjuvant (abstract, col 15-17, col 53, lines 10-55; col 54, lines 40-46). Classen also provides for various modes of injectable compositions for use in intramuscular or subcutaneous administration. (col 20, lines 56-60; col 52, lines 25-50). Classen does not explicitly describe the specific combination of an immunogen with a calcium phosphate, a cytokine and a secondary adjuvant.

Even though Reyveld and Poser fails to explicitly use cytokine or an additional adjuvant in their combined formulation, it would have been obvious to one of ordinary skill in the art at the time of invention to employ a cytokine or immunogenic adjuvant, as described by Classen, because addition of either or both cytokines and secondary adjuvants would have increased the specificity, the duration of exposure and further improved the induction of an immune response.

One of ordinary skill in the art would have had a reasonable expectation of success to further modify the Reyveld and Poser combination by adding a cytokine or a

secondary adjuvants because incorporation of such agents to improve the clinical effects of vaccine is well described in the art.

7. Claims 47-48, 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld US Patent 4,016,252 in view of Poser US Patent 5,968,253, Classen US Patent 5,723,283 as applied to claims 45-46, 49-54, 56-61, 64-72 and further in view of Lee US Patent 6,541,037

The combined teachings of Reyveld, Poser and Classen fails to teach calcium phosphate particles having a size range between of 0.1-900 nm and concentrations of about 25-100% by weight.

Lee's teachings are used for two reasons. First, Lee explicitly describes the significant of small calcium phosphate particle size for depot delivery systems. For example, Lee explains suitable particles within at least micron size for improved efficacy. (see figure 8 and example 5). Second, Lee also is used to show the understanding in the art that calcium phosphate delivery systems can not only be used to for delivery of antibiotics into the bone, but also as a delivery system in a vaccine formulation. (see abstract, col 16, lines 4-25; col 2,, lines 56-65; col 24, lines 33-56; col 30, lines 10-67; col 32-33). Thus, the use of calcium phosphate delivery systems in both art of drug delivery and vaccine delivery is viewed to be analogous.

Accordingly, absent a showing it would have been obvious to one of ordinary skill in the art at the time of invention to further optimize the particle size and/or concentration of calcium phosphate in Reyvelds vaccines by modifying its calcium

phosphate particle to nanometer ranges and/or the concentrations of such particles by routine experimentation to achieve the optimal clinical results.

Response to Arguments

8. Applicant's arguments with respect to rejection of claims over Poser, Reyveld and Classen have been considered but are moot in view of the new ground(s) of rejection. However, Examiner would respond to Applicant's central argument that Poser's teachings are not analogous to those of Reyveld and Classen and one of ordinary skill in the art of vaccine formulations would have not looked as Poser. (see Arguments at page 16, 3rd para.). In essence applicant appears to argue that Reyveld and Classen teach away from the teachings of Poser and thus the modification instantly reasoned.

9. Contrary to Applicant's position, Examiner states that the state of art at the time of invention does not discourage one of ordinary skill in the art of pharmaceutical drug delivery systems from referring to the teachings that discuss vaccine containing delivery formulations. Here, Applicant appears to misinterpret what it means to "teach away" from a patented invention. Generally, "disclosed examples and preferred embodiments do not constitute a teaching which is away from a broader disclosure or nonpreferred embodiments." *In re Susi*, 169 USPQ 423 (CCPA 1971). "In general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the results sought by the applicant." *In re Gurley,* 31 USPQ2d 1130, 1131-2 (Fed. Cir. 1994). In the instant case, the mere fact that there is an alternative means of improving drug delivery as described by Reyveld

does not preclude optimization of its formulations that is obvious over Classen and Poser.

10. Specifically, the portions of Reyveld's patent that Applicant characterizes as a "teaching away" (col 2, lines 2-9) does not discourage one of ordinary skill in the art to employ the paste formulations of Posner. Posner offers a new physical form of calcium phosphate drug carrier system for delivery into a specific site. There is nowhere in Poser's teachings prohibiting the use of his paste formulation for delivery of vaccines.

11. Second, Applicant has not provided any evidence or explains how the disclosures of the prior art show that their claimed invention is unlikely to be productive when Poser's paste formulation is used as a carrier system in place of Reyveld's. Simply, there is no statement in Reyveld or Poser showing that the instantly claimed physical characteristic would have been less attractive for delivery of vaccine. Therefore, Examiner concludes that a person of one ordinary skill, upon reading the cited reference, would not have been discouraged from combining them to improve vaccine delivery.

12. Moreover, Applicant's current position is at odds with his earlier obtained patent. As stated above, Applicant in his earlier US Patent 6,541,037 titled Delivery Vehicle, acquiesced to the fact that one of ordinary skill in the art can not only use calcium phosphate delivery systems for delivering antibiotics to bone, but also can use such delivery systems for delivering vaccines. Since such teaching was avaialbe to one of ordiary skill in the art prior to the effective filing date of the instant application, Applicant's current position set forth in response filed on March 24, 2005 seems to be at

adds with his teachings in the earlier obtained patent. Thus, Applicant's argument is contradictory in nature with his earlier positions.

13. Finally, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the teachings of Posner is reasonably pertinent to those of Reyveld and Classen, because it describes other forms of calcium phosphate delivery systems that have been shown to be safe and effective for in vivo use. For such reasons, Examiner maintains position that all cited references are analogous art.

Conclusion

No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action because it modified the scope of the claims. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SREENI PADMANABHAN
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